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(71) Applicant *(for all designated States except US)*: NAEJA PHARMACEUTICAL INC [CA/CA]; #2, 4290–91A Street, Edmonton, Alberta T6E 5V2 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SINGH, Rajeshwar [CA/CA]; Naeja Pharmaceutical Inc, 4290–91A Street, Edmonton, Alberta T6E 5V2 (CA). REDDY, Andhe, V., Narender [CA/CA]; Naeja Pharmaceutical Inc, 4290–91A Street, Edmonton, Alberta T6E 5V2 (CA). KALETA, Jadwiga [CA/CA]; Naeja Pharmaceutical Inc, 4290–91A Street, Edmonton, Alberta T6E 5V2 (CA). MICETICH, Ronald, G. [CA/CA]; Naeja Pharmaceutical Inc, 4290–91A Street, Edmonton, Alberta T6E 5V2 (CA). WHITTAKER, Mark [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). HUXLEY, Philip [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

(74) Agents: WALSH, David, Patrick et al.; Appleyard Lees, 15 Clare Road, Halifax HX1 2HY (GB).

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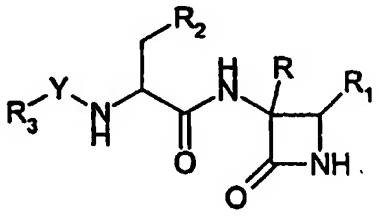
(54) Title: SUBSTITUTED AZETIDIN–2–ONES AS CYSTEINE PROTEASE INHIBITORS

(57) Abstract

This invention relates to substituted azetidin–2–ones and to pharmaceutical compositions containing such compounds. Their use in medicine as inhibitors of cysteine proteases, particularly the cathepsins is also described. The invention includes a compound of formula (I), Y represents –C(O)– or –S(O$_2$)– ; R represents an allyl (ie CH_2=$CHCH_2$–) group or a radical. R_1 represents –OCOR$_5$, –OR$_5$, –SR$_5$, –S(O)R$_5$, or –S(O)$_2$R$_5$; R_2 represents a radical. R_3 represents –OR$_5$ or R$_5$; or a pharmaceutically acceptable salt, hydrate or solvate thereof.



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Substituted Azetidin-2-ones As Cysteine Protease Inhibitors

This invention relates to substituted azetidin-2-ones, to pharmaceutical compositions containing such compounds, and to their use in medicine as inhibitors of cysteine proteases, particularly the cathepsins.

Background to the Invention

The cathepsin family (C1) of lysosomal cysteine (or thiol) proteases is a subset of the papain superfamily (clan CA of cysteine proteases) and includes cathepsin B, H, K, S, L and the recently discovered cathepsins O, O2/K, V, X, Z and W (lymphopain). Related enzymes also regarded as cysteine proteases are the cytoplasmic Ca^{2+} dependent calpains (family C2). Cysteine proteases are classified both functionally and according to their active site, which has a thiol residue. They differ in substrate specificities and other enzymatic activities, these differences probably arising from evolutionary divergence.

The known cathepsins are synthesized on membrane bound ribosomes, transferred to the endoplasmic reticulum, then to the Golgi apparatus and finally to the lysosome and endosomes. They have an important function in regulation of intracellular protein metabolism, mobilisation of tissue proteins and conversion of proenzymes, prohormones and neuropeptides into biologically active molecules. The cathepsins are believed to be involved in a number of diseases.

Cathepsin K can be secreted into the extracellular space and is involved in bone and cartilage remodelling. Cathepsin K is implicated in the pathogenesis of osteoporosis. Cathepsin K inhibitors can prevent osteoporosis in animal models (PNAS.1997. 94:14249-14254). Cathepsin L inhibitors have also been shown to inhibit osteoporosis (Bone, 1997. 20:465-471).

Cathepsin B and others have also been shown to be released extracellularly by

various tumour cells and are thought to play a role in tumour invasion (Journal of cellular Physiology. 1992. 150:534-544).

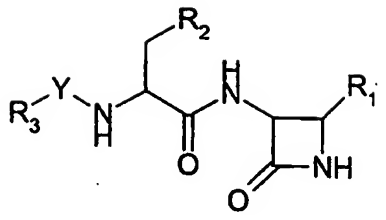
The cathepsins have also been shown to play a role in rheumatoid arthritis (Arthritis and Rheumatism 1994. 37:236-247) and neuronal and cardiac ischaemia (European Journal of Neuroscience. 1998. 10.1723-1733).

Cathepsins S and L both play a role in the generation of free MHC class II molecules capable of binding antigenic peptides in the endosomes. These class II/peptide complexes move to the cell membrane and are involved in T lymphocyte activation. Inhibitors of Cathepsin S have been shown to inhibit allergic immune responses (Journal of Clinical Investigation. 1998. 101:2351-2363).

In addition to their role in the above diseases, cathepsins play a major role in the pathogenesis of infectious diseases. For example, cathepsins are used by the protozoal parasites Plasmodium (malaria) and Trypanosoma (Chagas Disease) to invade the human host and cathepsin inhibitors can inhibit experimental disease in both cases (Antimicrobial agents and chemotherapy. 1998. 42:2254-2258; Journal of Experimental Medicine. 1998. 188:725-734). Cathepsins are also virulence factors for several pathogenic bacteria.

A recent review (Annu. Rev. Physiol. 1997. 59:63-88) describes the state of the art of cysteine proteases, including the cathepsins, and their presumed biological functions. Another review (Exp. Opin. Ther. Patents,1998, 8(6), pp645-672) deals with cathepsin B inhibitors as potential anti-metastatic agents.

International patent applications WO 96/32408, WO 98/12176, WO 98/12210 and GB 9806287.0 describe, inter alia, classes of cysteine protease inhibitors which may be represented by formula (IA):



(IA)

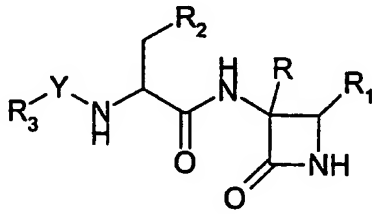
wherein Y, R_1, R_2 and R_3 represent the groups found in corresponding positions of the compounds disclosed in those publications. These known compounds are azetidin-2-ones which are monosubstituted at positions 3 and 4.

Brief Description of the Invention

The present invention makes available a new class of cysteine protease inhibitors which differ in structure from those disclosed in WO 96/32408, WO 98/12176, WO 98/12210 and GB 9806287.0 principally in that they are disubstituted at the 3-position. These compounds are useful for the treatment of diseases mediated by cysteine protease activity, for example muscular dystrophy, osteoporosis, tumour metastasis, rheumatoid arthritis, neuronal or cardiac ischaemia, allergic immune response, and protozoal or bacterial disease.

Detailed Description of the Invention

According to the present invention, there is provided a compound of formula (I)



(I)

Y represents -C(O)- or -S(O_2)-;

R represents an allyl (ie CH_2=$CHCH_2$-) group or a radical of formula R_4-$(ALK)_p$-$(Z)_n$-$(ALK)_q$- wherein Z represents -O- or -S-, ALK represents a divalent C_1-C_3alkyl or halogen-substituted C_1-C_3alkyl radical, R_4 represents hydrogen or halogen, or an

optionally substituted phenyl group, and n, p and q are independently 0 or 1, PROVIDED THAT (i) when R_4 is hydrogen and both p and n are 0 then q is 1; and (ii) when R_4 is halogen and n is 1 then p is 1; and (iii) when R_4 is halogen then p, n and q are not all 0;

R_1 represents $-OCOR_5$, $-OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

R_2 represents a radical of formula $R_6-(ALK)_p-(Z)_n-(ALK)_q-$ wherein p, Z and ALK are as defined in relation to R, q is 0 or 1, n is 0 or 1 when q is 1 and n is 0 when q is 0, and R_6 is hydrogen or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclic group; or R_2 together with the carbon atom to which it is attached forms a cycloalkyl ring;

R_3 represents $-OR_5$ or $-R_5$;

R_5 represents a radical of formula $R_7-(A)_t-$ wherein t is 0 or 1; A represents (i) an optionally substituted divalent C_1-C_6alkyl, radical which may be interrupted by one or more non-adjacent -O-, -S- or -NH- linkages, or (ii) a divalent C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclic radical, or (iii) a -NH- link; and R_7 represents hydrogen or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclic group;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Pharmaceutically acceptable salts of the compounds of this invention include the sodium, potassium, magnesium, calcium, hydrogen chloride, tartaric acid, succinic acid, fumaric acid and p-toluenesulfonic acid salts.

As used herein the term "(C_1-C_6)alkyl" or "lower alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl,

ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylprop-1-yl, 2-methylprop-2-yl, pentyl, 3-methylbutyl, and hexyl. Similar terms such as "(C_1-C_3)alkyl" are to be interpreted similarly.

As used herein the term "C_2-C_6alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl. Similar terms such as "(C_2-C_3)alkenyl" are to be interpreted similarly.

As used herein the term "C_2-C_6 alkynyl" means a straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. Similar terms such as "(C_2-C_3)alkynyl" are to be interpreted similarly.

As used herein the term "cycloalkyl" means a saturated alicyclic moiety having from 3-7 carbon atoms and includes, for example, cyclohexyl, cycloheptyl, cyclopentyl, cyclobutyl and cyclopropyl.

As used herein the term "halogen" means fluoro, chloro, bromo or iodo.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic, substituted or unsubstituted, carbocyclic aromatic group, and to groups consisting of two covalently linked substituted or unsubstituted monocyclic carbocyclic aromatic groups. Illustrative of such groups are phenyl, biphenyl and napthyl. Examples include C_6-C_{12} aryl groups such as phenyl, biphenyl, naphthyl, tetrahydronaphthyl, dihydronaphthyl, and cyclohexyl phenyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" means a 5-7 membered heterocyclic ring, which may be aromatic or non-aromatic, containing one or more heteroatoms selected from S, N and O, and optionally fused to a benzene or hetero-atom containing ring. The term therefore includes C_1-C_{11} heterocyclic groups containing 1-4 heteroatoms selected from nitrogen, sulfur or oxygen. Examples include thienyl, pyridyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, imidazolyl, quinolinyl, isoquinolinyl, indolyl, pyrimidinyl, benzofuranyl, benzothienyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, pyridylphenyl, pyrimidylphenyl, pyrrolyl, furyl, thienyl, piperidinyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, benzimidazolyl, maleimido, succinimido, and phthalimido groups.

As used herein, the unqualified term "substituted" as applied to a group or radical means substituted with 1, 2, or 3 substituents selected from

(C_1-C_3)alkyl;
phenyl;
hydroxy or mercapto;
(C_1-C_3)alkoxy or (C_1-C_3)alkylthio;
phenoxy or phenylthio;
halogen;
trifluoromethyl;
nitro;
cyano (-CN);
carboxyl, and amidated, esterified or protected carboxyl;
amino, mono- or di-(C_1-C_3)alkylamino, or protected amino;
(C_1-C_3)alkylcarbonyl- or (C_1-C_3)alkylcarbonylamino-;
-$CONHR^A$, -NHR^A, -NR^AR^B, or -$CONR^AR^B$ wherein R^A and R^B are independently (C_1-C_3)alkyl; and

-NH-C(=NR_8)R_9 wherein R_9 is amino, mono- or di-(C_1-C_6)alkylamino, protected amino, or (C_1-C_3)alkyl, and R_8 is hydrogen, (C_1-C_3)alkyl, or an N-protecting group.

As used herein the term "protecting group" when used in relation to an amino or carboxylic acid moeity in the compounds of this invention means a group which is used to render the amino or carboxylic acid moeity substantially non reactive, ie to neutralise its amino or carboxylic acid functionality. In this context, protected amino groups include amido and acylamino, protected hydroxy or mercapto groups include ethers and thioethers, protected carboxyl groups include esters, and imidazolyl, indolyl or guanidyl groups may be protected as t-butoxycarbonyl derivatives. These are only examples of the many protecting derivatives known in the art, and others will be known to the skilled man. Such protecting groups are of course well known, eg from the art of peptide synthesis, and are discussed in the widely used handbook by T.W. Greene and P.G.M. Wuts, Protective groups in Organic Synthesis, 2nd Edition, Wiley, New York 1991, and elsewhere in the chemical literature.

The azetidinone nucleus in the compounds of the invention has two asymmetric carbon atoms at position 3 (carrying the R group) and 4 (carrying the R_1 group), and can exist as 4- diastereoisomers. While the invention includes all such diastereomers and mixtures thereof (including racemic mixtures), compounds in which the R and R_1 groups are cis to each other are currently preferred, as are mixtures of diastereoisomers in which that configuration predominates.

As mentioned above, the compounds of the invention differ in structure from those of WO 96/32408, WO 98/12176, WO 98/12210 and GB 9806287.0 principally in that they carry a second substituent R at the 3-position of the azetidin-2-one ring. Thus the substituents R_1, R_2 and R_3 in the compounds of the invention may be any of the groups falling within the above definitions of R_1, R_2 and R_3 and which are present in corresponding positions of cysteine protease inhibitors disclosed in those patent

applications. Without prejudice to the generality of the foregoing, in the compounds of the invention:

Y may be, for example, -C(O)-;

R may be, for example, allyl, methyl; ethyl, n-propyl, n-or iso-butyl, methyoxymethyl, ethoxymethyl, benzyl, or phenoxymethyl;

R_1 may be, for example, acetoxy; butyloxy; 2-carboxyethyloxy; 2-aminoethyloxy; 2-fluoroethoxy; cyclopentyloxy; cyclohexyloxy; cyclohexylthio; phenoxy, phenoxy substituted by methyl, tert-butyl, trifluoromethyl, amino, hydroxy, acetamido, cyano, carboxy or fluoro; naphthyloxy; morpholino-phenyloxy; 2-hydroxyethylthio; phenylthio; phenylsulphonyl; 4-(2-carboxy-2-amino ethyl)-phenoxy; 2-pyridylthio; 4-pyridylthio; benzyloxy; 3-pyridyl-phenoxy; 3-tetrazolyl-phenoxy; 3,4-methylenedioxy-phenoxy; 3,4-ethylenedioxy-phenoxy; tetrahydroquinolinoxy; quinolinoxy; or quinolinthio. Currently preferred are acetoxy and phenoxy.

R_2 may be, for example, a phenyl group which may be substituted by one or more of hydroxy, halogen, methoxy, methyl, isopropyl, tert-butyl and trifluoromethyl; isopropyl, cyclohexyl; 3-pyridinyl; naphthyl; biphenyl; 2-thienyl; 3,4-methylenedioxyphenyl; 3,4-ethylenedioxy -phenyl; benzothienyl; thiazolyl; quinolinyl; isoquinolinyl; tetrahydroquinolinyl; tetrahydronaphthyl; aminonaphthyl; or acetamidonaphthyl. Presently preferred are phenyl, isopropyl, cyclohexyl and 3-pyridinyl.

R_3 may be, for example, benzyloxy, 3-phenylpropyloxy, 3-phenylpropyl, 3-phenylprop-1-enyl, 6-N,N-dibenzyloxycarbonylguanidino-hexyl, 6-guanidino-hexyl, methoxy-methyleneoxy-methyl, 2-amino-ethoxy-methyl, 3-(pyridin-3- or 4-yl)-propyl, or 3-(pyridin-3- or 4-yl)-prop-1-enyl.

Specific compounds of the invention include those of named and characterised in the Examples herein.

As stated, the compounds of the invention are inhibitors of cysteine proteases, for example cathepsins B, L, S and/or K. The invention therefore also provides a pharmaceutical composition containing a compound of formula (I) as defined above, and a pharmaceutically acceptable carrier. Also provided is the use of such a compound in the preparation of a composition for inhibiting cysteine protease activity in the body of a mammal suffering a disease mediated by such activity, and a method of treatment of an animal suffering from a disease mediated by cysteine protease activity, which method comprises administering to the mammal a sufficient amount of a compound of formula (I) as defined above to inhibit such activity.

Diseases mediated by cysteine protease activity include muscular dystrophy, osteoporosis, tumour metastasis, rheumatoid arthritis, neuronal or cardiac ischaemia, allergic immune response, and protozoal or bacterial disease.

Compositions with which the invention is concerned may be prepared for administration by any route consistent with the pharmacokinetic properties of the active ingredient(s).

Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be

coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

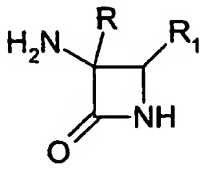
For topical application to the skin, the active ingredient(s) may be made up into a cream, lotion or ointment. Cream or ointment formulations, which may be used for the drug, are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

The active ingredient(s) may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. Intravenous infusion is another route of administration for the compounds.

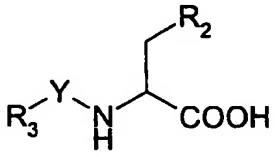
Safe and effective dosages for different classes of patient and for different disease states will be determined by clinical trial as is required in the art. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing

therapy.

Compounds of the invention may be prepared by acylation of the 3-amino group of a compound of formula (II) with an acylating derivative of a compound of formula (III)



(II)

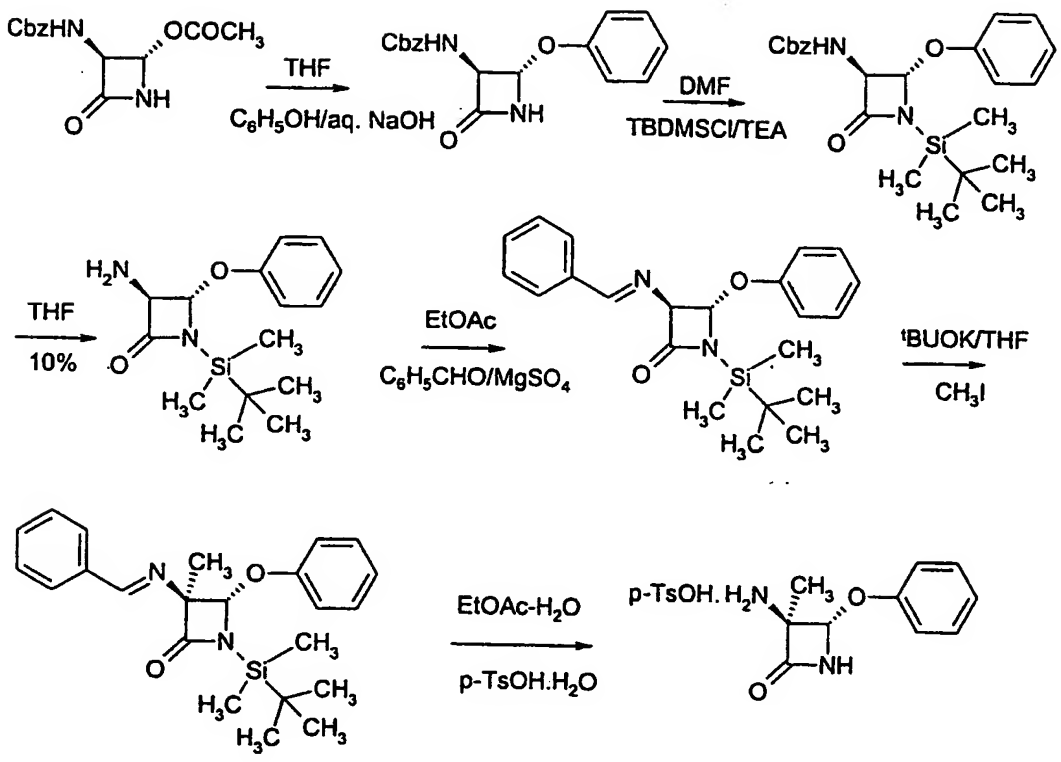


(III)

wherein Y, R, R_1, R_2 and R_3 are as defined above except that any functional groups present in R, R_1, R_2 and R_3 which might give rise to substantial amounts of unwanted by-products are protected, and thereafter removing any such protecting groups. In the acylation reaction, compound (III) may be activated as an active ester, for example the hydroxybenzotriazolyl ester, to facilitate the acylation reaction.

Compounds (II) are accessible from commercially available materials by widely known synthetic methods. Reaction Schemes 1 and 2 below illustrate synthetic routes to compounds (II) in which R is methyl, which may be modified as appropriate to produce other compounds of formula (II). Compounds (III) are in many cases commerially available, and otherwise are also accessible from commercially available materials by widely known synthetic methods.

Scheme 1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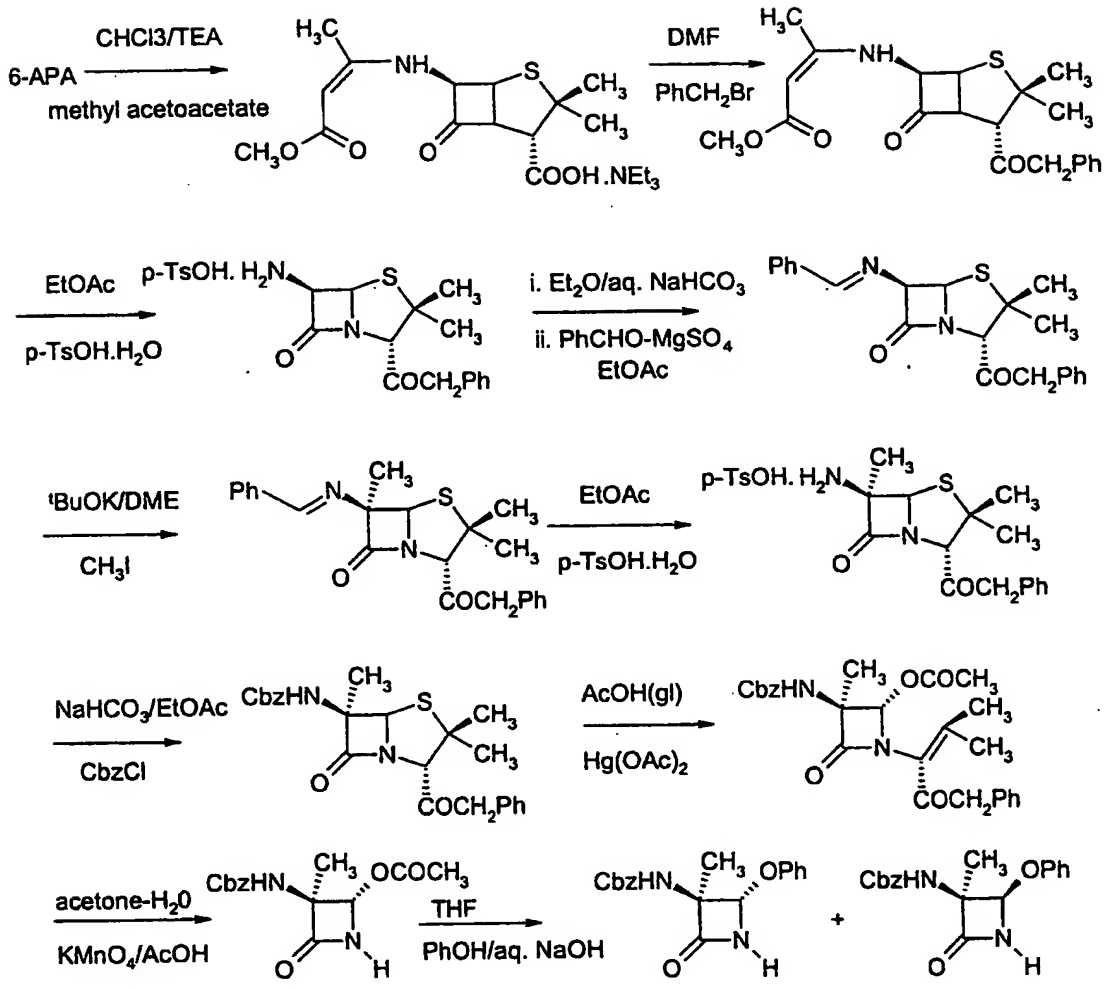
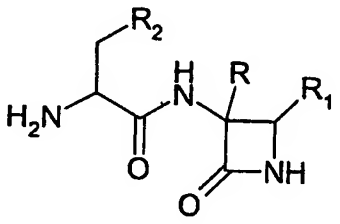
OCOCH3
NH
O
THF
C6H5OH/aq. NaOH
DMF
TBDMSCl/TEA
CH3
Si
H3C
H2N
10%
EtOAc
C6H5CHO/MgSO4
tBUOK/THF
CH3I
EtOAc-H2O
p-TsOH.H2O
p-TsOH. H2N

Scheme 2

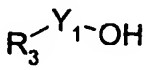

CHCl3/TEA
6-APA
methyl acetoacetate
DMF
PhCH2Br
EtOAc
p-TsOH.H2O
i. Et2O/aq. NaHCO3
ii. PhCHO-MgSO4
EtOAc
tBuOK/DME
CH3I
EtOAc
p-TsOH.H2O
NaHCO3/EtOAc
CbzCl
AcOH(gl)
Hg(OAc)2
acetone-H2O
KMnO4/AcOH
THF
PhOH/aq. NaOH

An example of an acylation reaction between a compound of formula (II) and a compound of formula (III) is shown in Scheme 3. In general, the amine (II) and the acid (III) are coupled either in presence of coupling reagent or by use of the chloride or anhydride of (III) in presence of base or activated ester.

In some cases, compounds of formula (I) may be prepared by coupling a compound of formula (IV) with a compound of formula (V):



(IV)



(V)

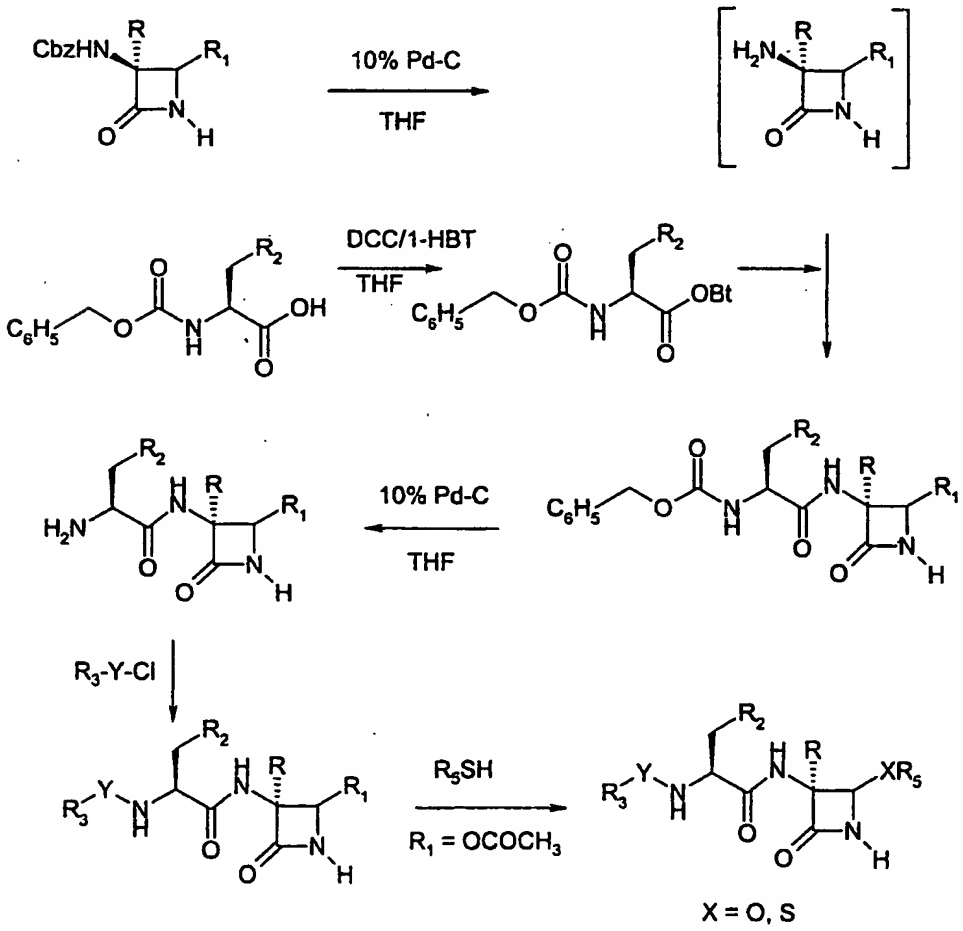
wherein Y_1 represents -CO- or -$S(O)_2$-, and R, R_1, R_2 and R_3 are as defined above except that any functional groups present in R, R_1, R_2 and R_3 which might give rise to substantial amounts of unwanted by-products are protected, and thereafter removing any such protecting groups. Here again the amine (IV) and the acid (V) (Y_1 = -CO-) are coupled either in presence of coupling reagent or by use of the chloride or anhydride of (V) in presence of base, or by use of an activated ester.

Compounds (V) are in many cases commerially available, and otherwise are accessible from commercially available materials by widely known synthetic methods.

In some cases, one compound of formula (I) may be prepared from another of formula (I). For example, Scheme 3 shows a synthetic route in which the 4-acetoxy group in a compound of formula (I) wherein R_1 is acetoxy is converted to a group –

OR_5 or $-SR_5$. Conversion of the 4-acetoxy group is effected by reacting with R_5XH in presence of lewis acids such as zinc acetate, zinc iodide, zinc chloride, titanium tetrachloride, palladium acetate, boron trifluoride, aluminium trichloride and the like or in presence of base such as sodium hydroxide. Reactive groups in R_5 will of course be protected during such reactions, and subsequently deproteced. Thus, where a carboxy group is present in R_5 it may be protected with diphenyl methyl or 1,1-dimethyl ethyl and an amino group in R_5 may be protected with benzyloxycarbonyl or 1,1-dimethylethoxycarbonyl. Deprotection may be effected by hydrogenation or hydrolysis with acids.

Scheme 3



Monobactam derivatives of general formula I wherein R_1 is $-SR_5$ may be converted to, $-SOR_5$, or $-SO_2R_5$ by oxidation with oxidizing agent such as m-chloroperbenzoic acid, hydrogen peroxide. peracetic acid, potassium permanganate, or manganese dioxide.

The following Examples illustrate embodiments of the invention.

Example-1

(3S, 4S)- 3-[2S-2-(benzyloxycarbonylamino)-2-benzyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one

Step-1: (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-benzyloxycarbonylamino-4-phenoxy-azitidine-2-one

A solution of 3-(S)-benzyloxycarbonylamino-4-(R)-phenoxy-azitidine-2-one (5.05g, 16.17mmol) in dry dimethyl formamide (50ml) under nitrogen was treated with tert-butyl dimethylsilyl chloride (2.93g, 19.40 mmol) at room temperature. The reaction mixture was added with triethyl amine (2.454g, 24.3mmol) with in 10 min. and stirred at room temperature for 1.5h. The suspension obtained was filtered and the filtrate was concentrated *in vacuo* to give a gummy mass. The gum obtained was dissolved in ethyl acetate (200ml), washed with water (2x100ml), brine (100ml), dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a foamy gum. Purification of the above crude product over silica gel column using a mixture of hexane:ethyl acetate (9:1) gave the pure compound as a viscous oil (6.1g).

Yield: 88.4%.

^{1}H NMR (DMSO-d_6): ä 0.23 and 0.26(2s, 6H), 0.97(s, 9H), 4.44(d, 1H, J=9.0 Hz), 5.11(ABq, 2H, J=1.0 and 13.9.0Hz), 5.55(s, 1H, C4H), 6.82-7.39(m, 10H) and 8.35(d,

1H, 8.3 Hz)

Step-2: (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-amino-4-phenoxy-azitidine-2-one

(3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-benzyloxycarbonylamino-4-phenoxy-azitidine-2-one (7.77g, 18.22mmol) and 10% Pd-C (50% wet, 7.7g) in a mixture of EtOAc-THF (1:1, 200ml) was hydrogenated at 50psi for 2.5 hrs and filtered through Celite. The filtrate was evaporated *in vacuo* and dried over the pump to give a clear, sticky oil, which was purified over a small silica gel column using hexane: EtOAc (8:2 to 1:1) to give pure compound (4.89g) as an oil.

Yield: 91.8%.

^{1}H NMR (DMSO-d_6): ä 0.18 and 0.26(2s, 6H), 0.96(s, 9H), 2.55(s, 2H), 3.88(t, 1H, J=8.6 Hz), 5.15(d, 1H, J=0.9 Hz) and 6.97-7.38(m, 5H).

Step-3: (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3- benzylideneimino-4-phenoxy-azitidine-2-one

To a suspension of (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-amino-4-phenoxy-azitidine-2-one (4.89g, 16.72mmol) in dry benzene (80ml) and magnesium sulfate (anhyd., 20g.) was added benzaldehyde (1.952g, 18.393mmol) and the mixture was stirred under nitrogen for 24 hrs. The suspension was filtered and the filtrate was evaporated *in vacuo* to give an oil, which was dissolved in EtOAc (200ml). The EtOAc solution was washed with water (2x150ml), sodium bisulfite (10%, 2x 150ml), brine (200ml), dried over magnesium sulfate, filtered and evaporated in vacuo to give the title compound as a thick and clear oil (6.2g).

Yield: 97.5%.

^{1}H NMR (DMSO-d_6): ä 0.25 and 0.30(2s, 6H), 0.99(s, 9H), 4.91(s, 1H), 5.73(s, 1H),

6.85-7.85(m, 10H) and 8.51(s, 1H).

Step-4: (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3- benzylideneimino-3-methyl-4-phenoxy-azitidine-2-one

(3S, 4S)-1-(N-tert-butyldimethylsilyl)-3- benzylideneimino-4-phenoxy-azitidine-2-one (2.017g, 5.3mmol) in dry THF under nitrogen was cooled to B 40 °C and treated with potasium-tert-butoxide (0.654g, 5.8302mmol) in one portion. After stirring for 15 min., was added methyl iodide (0.828g, 5.8302mmol) to the orange-red colored reaction mixture and was stirred for 20 min. at B 40 °C. The reaction mixture was quenched with 2ml.of sat. ammonium chloride solution, stirred for 5 min. and diluted with ethyl acetate (100ml). The EtOAc solution was washed with water (2x 10ml), brine solution (100ml), dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to give a gum, which was purified over a silica gel column at ~10 °C, using a mixture of hexane:ethyl acetate (4:1) to give the pure compound as an oil (0.498g).

Yield: 23.8%.

^{1}H NMR (DMSO-d_6): ä 0.20 and 0.26(2s, 6H), 0.96(s, 9H), 1.37(s, 3H), 5.53(s, 1H), 6.97-7.88(m, 10H) and 8.63(s, 1H).

Step-5: (3S, 4S)-3-amino-3-methyl-4-phenoxy-azitidine-2-one. p-TsOH

To a solution of (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3- benzylideneimino-3-methyl-4-phenoxy-azitidine-2-one (0.528g, 1.34mmol) in ethyl acetate (15ml) was added p-TsOH, H_2O, followed by dd. Water (3ml). The reaction mixture was vigorously stirred at 35 °C for 4 h. and the resulting suspension was filtered, washed with cold EtOAc, ether and dried to give a white solid.

^{1}H NMR (DMSO-d_6): ä 1.51(s, 3H), 2.29(s, 3H), 5.64(s, 1H), 6.98-7.50(m, 9H), 8.94(br

s, 3H) and 9.80(s, 1H).

Step-6: (3S, 4S)- 3-[2S-2-(benzyloxycarbonylamino)-2-benzyl-acetamido]-3-methyl-4-phenoxy azetidin-2-one.

A mixture of N-carbobenzyloxy phenyl alanine (0.093g, 0.31mmol), DCC (0.064g, 0.31mmol) and 1-HBT (0.042g, 0.31mmol), in dry THF (10ml) under nitrogen was stirred at room temperature for 1h. The (3S, 4S)- 3-[2S-2-(benzyloxycarbonylamino)-2-benzyl-acetamido]-3-methyl-4-phenoxy azetidin-2-one. P-TsOH salt (0.107g, 0.2936mmol) was dissolved in DMF (8ml) treated with triethyl amine (46ul) and the clear solution obtained was added to the reaction mixture. After stirring for 1.5 h. the suspension was filtered and the filtrate was evaporated *in vacuo* to give a gummy crude product. The above gummy product was dissolved in EtOAc (80ml), washed with aq. sat. $NaHCO_3$, brine solution, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The crude product obtained was purified over silica gel column chromatography using a mixture of hexanes:ethyl acetate (1:1) to give the pure title compound (85mg)

m.p.: 76.5-78 °C

^{1}H NMR (DMSO-d_6): ä 1.32(s, 3H), 2.73-3.09(m, 2H), 4.35-4.45(m, 1H), 4.96(ABq, 2H, J=2.0 Hz), 5.56(s, 1H), 6.82-7.39(m, 15H), 7.56(d, 1H, J=8.8 Hz), 8.55(s, 1H) and 9.15(s, 1H).

Example-2

(3S, 4S)-3-[2S-2-(benzyloxycarbonylamino)-2-isopropyl]-acetamido-3-methyl -4-phenoxy azetidin-2-one

A mixture of N-carbobenzyloxy leucine (0.083g, 0.313mmol), DCC (0.065g, 0.313mmol)

and 1-HBT (0.043g, 0.313mmol), in dry DMF (10ml) under nitrogen was stirred at room temperature for 1h. (3S, 4S)-3-amino]-3-methyl-4-phenoxy azetidin-2-one. p-TsOH salt (0.114g, 0.313mmol) was added to the reaction mixture followed by triethyl amine (48ul, 0.035g, 0.313mmol) and stirred for an additional 3 h. The mixture was evaporated *in vacuo* and the crude product obtained was dissolved in EtOAc (80ml), washed with water, brine solution, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to give the crude product. Purification of the above crude product by silica gel column chromatography using a mixture of hexanes:ethyl acetate (1:1) gave the pure title compound (88mg)

Yield: 66.2 %; m.p: 84.5-85 ^{0}C

^{1}H NMR (DMSO-d_6): ä 0.88(d, 3H, J=6.2Hz), 0.91(d, 3H, J=6.4Hz), 1.32(s, 3H), 1.00-1.80(m, 3H), 4.15-4.25(m, 1H), 5.03(ABq, 2H), 5.60(s, 1H), 6.85-7.35(m, 10H), 7.45(d, 1H, J=8.5Hz), 8.47(s, 1H), 9.12(s, 1H).

Example-3

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-isopropyl]-acetamido-3-benzyl -4-phenoxy azetidin-2-one

Step-1: (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-benzylideneimino-3-benzyl-4-phenoxy-azitidine-2-one

(3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-benzylideneimino-4-phenoxy-azitidine-2-one (1.622g, 4.262mmol) in dry THF under nitrogen was cooled to B 60 ^{0}C and treated with potasium-tert-butoxide (0.574g, 5.115mmol) in one portion. After stirring for 15 min., was added benzyl bromide (0.8g, 4.69mmol) to the orange-red colored reaction mixture and was allowed to come to 0 ^{0}C over 30 min. The reaction mixture was quenched with ice-water and diluted with ethyl acetate (100ml). The EtOAc solution was washed with

water (2x 10ml), brine solution (100ml), dried over anhydrous sodium sulfate, filtered and evaporated in vacuo to give a gummy oil (1.26g).
Yield: 62.8%

Step-2: (3S, 4S)-3-amino-3-benzyl-4-phenoxy-azitidine-2-one.

To a solution of (3S, 4S)-1-(N-tert-butyldimethylsilyl)-3-benzylideneimino-3-benzyl-4-phenoxy-azitidine-2-one (1.26g, 2.68mmol) in a mixture of ethyl acetate (20ml) and water (10ml) was added p-TsOH. H_2O (1.53g, 8.03mmol). The reaction mixture was vigorously stirred at r.t. for 48 h and the organic layer was separated. The aqueous layer was diluted with water (20ml), washed with hexanes and freeze dried to give give the crude p-TsOH salt of (3S, 4S)-3-amino-3-benzyl-4-phenoxy-azitidine-2-one which is contaminated with p-TsOH.
The above crude product was suspended in dd.H_2O (10ml), adjusted to pH ~10 with aq.sat. $NaHCO_3$ and extracted with ethyl acetate (2x50ml). The EtOAc extracts were pooled together, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo to give 3-(S)-amino-3-benzyl-4-(R)-phenoxy-azitidine-2-one, as a white solid (0.36g)

Yield: 50.1%; m.p.: 170-172 ^{0}C

^{1}H NMR (DMSO-d_6): ä 2.05(s, 2H), 3.02(ABq, 2H, J=4.3 and 15.9), 5.41(s, 1H, C4H), 6.80-7.39(m, 10H) and 8.93(s, 1H).

Step-3: (3S, 4S)-3-benzyloxy carbonylamino-3-benzyl-4-phenoxy azetidine-2-one.

A solution of (3S, 4S)-3-amino-3-benzyl-4-phenoxy-azitidine-2-one (0.1g, 0.373mmol) in THF (8ml) was treated with benzyloxy carbonyl chloride (0.072g, 0.42mmol) at room temperature and was added aq. $NaHCO_3$ (0.063g, 0.746mmol in 5ml water). The resulting suspension was stirred vigorously at room temperature over 20 hrs., diluted with EtOAc (25ml) and water (10ml). The organic layer was separated, washed

sequentially wih 1N. HCl (25ml), aq. sat. $NaHCO_3$ (2x25ml), brine solution and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave a gummy mass, which was purified over silica gel column to give (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-benzyl-4-phenoxy azetidine-2-one (0.86g).

Yield: 57%; m.p.: 64-65 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 3.24(ABq, 2H, J=6.6 and 17.0), 4.95(d, 1H, J=12.9 Hz), 5.12(d, 1H, J=12.9 Hz), 5.34(s, 1H), 6.72-7.30(m, 15H), 7.72(s, 1H) and 9.02(s, 1H).

Step-4: 3(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-isopropyl]-acetamido-3-benzyl -4-phenoxy azetidin-2-one

A mixture of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-benzyl-4-phenoxy azetidine-2-one (0.115g, 0.43mmol), N-carbobenzyloxy leucine (0.114g, 0.43mmol), DCC (0.089g, 0.43mol) and 1-HBT (0.058g, 0.43mmol) in dry THF (30ml) under nitrogen was stirred at room temperature for 6h. The suspension obtained was filtered and the filtrate was concentrated to give a gum, which was dissolved in EtOAc(80ml), washed with aq. sat. $NaHCO_3$ (80ml), brine solution, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo to give the crude product. Purification of the above crude product by silica gel column chromatography using a mixture of hexanes:ethyl acetate (3:2) gave the pure title compound (0.075g).

Yield: 34%; m.p.: 80.5-81.5 ^{0}C

^{1}H NMR (DMSO-d_6): ä 0.80-0.88(m, 6H), 1.25-1.70(m, 3H), 3.24(d, 1H, J=11.0 Hz), 3.50(d, 1H, J=11.0 Hz), 4.10-4.22(m, 1H), 5.06(ABq, 2H), 6.80-7.52(m, 16H) and 9.15(s, 1H).

Example-4

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one

Step-1: Preparation of benzyl-6-amino-penicillinate p-TsOH salt.

A suspension of 6-amino penicillanic acid (103.68g, 0.4794mol) in dry chloroform (1.2L) under nitrogen was treated with triethyl amine (97.02g, 0.959mol) at room temperature. The reaction mixture was stirred for 5 hrs, and to the clear solution obtained was added methyl acetoacetate, stirred at room temperature for 16 hrs.and evaporated *in vacuo*. The gummy mass obtained was dissolved in dry dimethy formamide (350ml) and benzyl bromide was added drop wise. After stirring for 8 hrs at room temperature was added 1.5L of ether. The suspension obtained was filtered and the filtrate was washed with water (5x1L) followed by aq. sat. sodium bicarbonate solution (2x1L), brine (1L0, dried over anhyd. magnesium sulfate, filtered and evaporated in vacuo to give a gummy product. The above gummy product was dissolved in ethyl acetate and was added p-toluene sulfonic acid monohydrate in portions. After stirring at room temperature for 2 hrs the resulting suspension was filtered, washed with ether followed by hexanes and air dried to give a white solid (136.56 g).

Yield: 92.25%.

Step 2: Preparation of benzyl-6-(benzylidene)-imino-penicillanate.

A suspension of benzyl-6-amino penicillin p-toluene sulfonate (118g, 0.2466mol) in ethyl acetate (1L) was treated with aq. sat. $NaHCO_3$ (1L) and stirred at room temperature for 1 hr. The organic layer was separated, washed brine solution (600ml), dried over anhyd. magnesium sulfate, filtered and concentrated to 800ml.

To the ethyl acetate solution was added anhydrous magnesium sulfate (200g) followed by banzaldehyde (28.141g, 0.2652mol) and the resulting suspension was stirred under nitrogen at room temperature for 16hrs. The suspension was filtered, washed with aq. sodium bisulfite (10%, 2x500ml)) followed by aq.sat.sodium bicarbonate (600ml), brine solution (600ml) and dried over magnesium sulfate. Filtration followed by evaporation of the solvent in vacuo gave the desired product semi solid (92g)

Yield: 96.8%

^{1}H NMR (DMSO-d_6): ä 1.38 and 1.58(2s, 6H), 4.42(s, 1H), 5.22(ABq, 2H, J=1.4 Hz and 12.3 Hz), 5.57(dd, 1H, J=2.58 and 1.6Hz), 5.67(d, 1H, J=4.3 Hz), 7.30-7.80(m, 10H) and 8.55(d, 1H, J=1.6 Hz).

Step 3: Preparation of benzyl-6-amino-6-methyl-penicillin p-TsOH salt.

A solution of benzyl 6-(benzylidene)-imino-penicillanate (72.7g, 184.33mmol) in dry dimethoxy ethane (375ml) under nitrogen was cooled to B60 °C. To the solution was added potassium tert-butoxide (21.424g, 190.76mmol) in portions over 20 min. and the resulting orange-red colored slurry was stirred for 30min. Then was added methyl iodide (52.33g, 369.2mmol) and the reaction mixture was allowed to come to 20 °C over 1h and quenched with 10ml water. The reaction mixture was diluted with ethyl acetate (1.3LI), washed with water (4x100ml), brine solution, dried over magnesium sulfate, filtered and evaporated *in vacuo* to give a gummy product (70.66g, 93.8%).

The above gummy product was dissolved in ethyl acetate (800ml) and was added p-toluene sulfonate (36.19g, 190mmol) portion resulting in the separation of a solid instantly. After stirring for 2 hrs. at room temperature the suspension was filtered washed sequentially with cold(~6 °C) ethyl acetate, ether followed by hexanes and air dried to give a white solid (56.4g).

Yield: 66.2%.

^{1}H NMR (DMSO-d_6): ä 1.38(s, 3H), 1.68 and 1.61(2s, 6H), 2.29(s, 3H), 4.58(s, 1H), 5.23(s, 2H), 5.41(s, 1H), 7.10-7.50(m, 9H), 8.83(br s, 3H).

Step 4. Preparation of benzyl 6-(N-benzyloxycarbonyl)-amino-6-methy-penicillanate

Benzyl-6-amino-6-methyl-penicillin p-TsOH salt (22.1g, 44.862mol)was suspended in a mixture of ethyl acetate (250ml) and dd. Water (170ml) and was treated with sodium bicarbonate(s) over 10 min. After stirring for 15 min., the mixture was treated with benzyloxy carbonyl chloride and stirred vigorously at room temperature for 2.5 hrs. The resulting mixture was diluted with brine solution (150ml), ethyl acetate (100ml) and the organic layer was separated. The ethyl acetate solution was washed sequentially with aq. sat. $NaHCO_3$, water, 1N. HCl, water, brine, dried over sodium sulfate and filtered. Evaporation of the solvent in vacuo resulted in the desired product as a sticky oil (20.2g)

Step 5: Synthesis of N-[(2-carboxybenzyl-1-propylidene)1-yl]3-(benzyloxycarbonyl)-amino-3-methyl-4-(R)-phenoxy-azetidine-2-one.

A solution of benzyl 6-(N-benzyloxy carbonyl)-amino-6-methy-penicillanate (7.14g, 15.71mmol) in glacial acetic acid (35ml) was treated with mercuric acetate(10.01g, 31.42mmol). The suspension was then stirred at 75 0C for 1.15h and cooled to room temperature. The slurry was filtered and the filtrate was concentrated in vacuo. The residue obtained was diluted with ethyl acetate (200ml), washed with cold water (2x200ml), aq. sat. $NaHCO_3$ (2x200ml), water, brine solution and dried over sodium sulfate. Filtration followed by evaporation of the solvents in vacuo gave an oil (6.67g, 88.3%), which upon purification over a silica gel column gave the desired compound (2.4g), as a sticky oil.

Yield: 31.8%.

^{1}H NMR (DMSO-d_6): ä 1.19(3s, 3H), 1.99(s, 6H), 2.15(s, 3H), 5.03(s, 2H), 5.15(d, 2H, J=2.0 Hz), 6.30(s, 1H), 7.31-7.77(m, 10H), 8.05(s, 1H).

Step-6: (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-acetoxy azetidine-2-one.

The starting material (15.84g, 32.97mmol) from step-5 was dissolved in a mixture of acetone (60ml), acetic acid (35ml) and water (75ml) and was cooled to ~5 ^{0}C in an ice-water bath. To the above reaction mixture was added solid $KMnO_4$ (7.82g, 49.46mmol) in portions and the resulting solution was stirred for 45 min. at ~5 0C, then diluted with ethyl acetate (250ml). The reaction was quenched with hydrogen peroxide (~30%) solution and the organic layer was separated. The aqueous layer was re-extracted with ethyl acetate and the combined organic extracts were pooled together, washed with aq. sat. $NaHCO_3$ (3x200ml), water, brine and dried over magnesium sulfate. Filtration followed by evaporation of the solvent *in vacuo* gave a sticky foam, which was purified over silica gel column (hexane:EtOAc/ 1:1) to give the title compound as solid(6.3g).

Yield: 47.8%; m.p.: 150-151 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.24(s, 3H), 2.09(s, 3H), 5.04(s, 2H), 5.96(s, 1H), 7.37(s, 3H), 7.91(s, 1H) and 8.98(s, 1H).

Step-7: (3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-acetoxy azetidine-2-one (0.35g, 1.1974mmol) in dry THF (30ml) was hydrogenated in presence of 10%Pd-C(50% wet, 0.35g) at 50psi over 2 hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-N-(3-phenylpropionyl)amido phenyl alanine in dry THF, which is prepared by the reaction of N-(3-phenylpropionyl)-amino phenyl alanine (0.356g, 1.1974mol) in (30ml), with DCC (0.247g, 1.1974mmol) and 1-HBT (0.162g,

1.1974mmol) at 10 ^{0}C and stirring for 1 hr. The reaction mixture was stirred at room temperature for 1 hr. and evaporated in vacuo to give the crude product. The above crude compound was purified over silica gel column, using a mixture of hexane:ethyl acetate(3:2) to give (3S, 4S)-3-[2S-2-(3-phenylpropionyl)amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one (0.32g).

Yield: 61.1%; m.p.: 92-93 ^{0}C

^{1}H NMR (DMSO-d_6): ä 1.26 (s, 3H), 2.10 (s, 3H), 2.32-3.00(m, 6H), 4.60-4.71(m, 1H), 5.85(s, 1H), 7.10-7.28(m, 10H), 8.10(d, 1H, J=8.5 Hz), 8.43 (s, 1H), 9.00(s, 1H).

Example-5

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one.

Step-1: (3S, 4SR)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-ones: A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-acetoxy azetidine-2-one (3.383g, 11.574mmol) in a mixture of tetrahydrofuran(40ml) and water(10 ml) was cooled to 0 0C and treated with an aqueous NaOH(0.509g, 15ml of water)solution of phenol(1.31g, 13.89mmol)drop wise over 10 min. The resulting solution was stirred at 0 0C for 1h., at room temperature for 2 hrs., and diluted with ethyl acetate(150ml) and water(10ml). The aqueous layer was separated and the organic layer was washed with brine dried over sodium sulfate and filtered. Evaporation of the solvent *in vacuo* gave a gummy foam, which on purification over silica gel column (hexanes:ethyl acetate/ 2:3) resulted in the isolation of two diasteriomers.

a). (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (1.53g).

Yield: 40.5%; m.p.:64-65 ^{0}C

^{1}H NMR (DMSO-d6): ä 1.30(s, 3H), 5.07(s, 2H), 5.66(s, 1H), 6.87-7.38(m, 10H), 8.05(s, 1H) and 9.14(s, 1H).

b). (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (1.37g).

Yield: 36%; m.p.: 69-71 ^{0}C

^{1}H NMR (DMSO-d_6): ä 1.46(s, 3H), 5.01(ABq, 2H, J=19.0 Hz and 12.8 Hz), 5.45(s, 1H), 6.75-7.33(m, 10H), 7.64(s, 1H) and 9.00(s, 1H).

Step 2: (3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.5g, 1.532mmol) in dry THF (25ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.5g) at 50psi over 3hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-N-(3-phenyl propionyl)-amino phenyl alanine in dry THF, which is prepared by the reaction of N-(3-phenylpropionyl)-amino phenyl alanine (0.456g, 1.532mmol) in THF (20ml), with DCC (0.316g, 1.532mmol) and 1-HBT (0.207g, 1.532mmol) at 10 0C and stirring for 1 hr. The reaction mixture was stirred at room temperature for 1 hr. and evaporated *in vacuo* to give the crude product. The above crude compound was purified over silica gel column, using a mixture of hexane:ethyl acetate(3:2 to 2:3) to give (3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one (0.51g).

Yield: 70.5%; m.p.: 163-164 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.29(s, 3H), 2.34-2.94(m, 6H), 4.65-4.75(m, 1H), 5.51(s, 1H),

6.79-7.35(m, 15H), 8.18(d, 1H, J=8.5 Hz), 8.54(s, 1H) and 9.14(s, 1H).

Example-6

(3S, 4R)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one

A solution of (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.52g, 1.5934mmol) in dry THF (30ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.5g) at 50psi over 4hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-N-(3-phenylpropionyl)-amino phenyl alanine in dry THF, which is prepared by the reaction of N-(3-phenylpropionyl)-amino phenyl alanine (0.474g, 1.5934mmol) in THF (20ml), with DCC (0.329g, 1.5934mmol) and 1-HBT (0.215g, 1.5934mmol) at 10 °C and stirring for 1hr. The reaction mixture was stirred at room temperature for 2 hr. and evaporated *in vacuo* to give the crude product. The above crude compound was purified over silica gel column, using a mixture of hexane:ethyl acetate (1:1 to 3:7) to give (3S, 4R)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one (0.56g)

Yield: 74.6%.; m.p.:204-206 °C.

^{1}H NMR (DMSO-d_6): ä 1.54(s, 3H), 2.24-2.66(m, 6H), 4.50-4.63(m, 1H), 5.46(s, 1H), 6.81-7.34(m, 15H), 8.16(d, 1H, J=8.9 Hz), 8.27(s, 1H) and 9.04(s, 1H).

Example-7

(3S, 4S)-3-[2S-2-(6-N, N-dibenzyloxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.425g, 1.3023mmol) in dry THF (20ml) was hydrogenated in presence of 10%Pd-C(50% wet, 0.4g) at 50psi over 2 hrs. The resulting suspension was filtered through Celite in to a pre-filtered solution of benzotriazolyl-2-[6-(N,N-dibenzyloxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetate, prepared by reacting 2-[6-(N,N-dibenzyloxycarbonyl-guanidinohexanoyl)-amino-2-cyclohexylmethyl]-acetic acid (0.775g, 1.3023mmol) in dry THF (20ml) with DCC (0.269g, 1.3023mmol) and 1-HBT (0.176g, 1.3023mmol) under nitrogen at 10 0C and stirring for 2hrs. The reaction mixture was stirred at room temperature for 2 hrs. and evaporated *in vacuo* to give the crude product. Purification of the above crude product over silica gel column, using a gradient mixture of hexane:ethyl acetate(1:1 to 3:7) gave the title compound (0.388g).

Yield: 38.8%, m.p.: 76-77 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 0.80-1.70(m, 22H), 2.10-2.20(m, 2H), 3.25-3.35(m, 2H), 4.40-4.50(m, 1H), 5.03(s, 2H), 5.21(s, 2H), 5.61(s, 1H), 6.85-7.41(m, 15H), 7.95(d, 1H, J=9.0 Hz), 8.40(s, 2H), 9.10(s, 1H), 1.60(s, 1H).

Example-8

(3S, 4R)-3-[2S-2-(tert-butoxycarbonyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one.

A solution of (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.775g, 2.3748mmol) in dry THF (25ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.77g) at 50psi over 2.5 hrs. The resulting suspension was filtered through Celite in to a pre-filtered solution of benzotriazolyl-2-(N-tert-butoxycarbonyl)-amino-2-cyclohexyl methyl acetate, prepared by reacting 2-(N-tert-butoxycarbonyl)-amino-2-

cyclohexyl methyl acetic acid (0.651g, 2.3748mmol) in dry THF (25ml) with DCC (0.515g, 2.3748mmol) and 1-HBT (0.337g, 2.3748mmol) under nitrogen at 10 °C and stirring for 1 hr. The reaction mixture was stirred at room temperature for 2hrs., and evaporated *in vacuo*. The crude product thus obtained was purified over silica gel column using a gradient mixture of hexane:ethyl acetate (1:1 to 3:7) to give the title compound (0.52g) as a white foam.

Yield: 66.2%; m.p.: 107-108 °C.

^{1}H NMR (DMSO-d_6): ä 0.60-1.70(m, 25H), 3.96-4.12(m, 1H), 5.39(s, 1H), 6.67-7.32(m, 6H), 7.95(s, 1H) and 8.98(s, 1H).

Example-9

(3S, 4R)-3-[2S-2-(6-N, N-dibenzyloxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one

Step-1: (3S, 4R)-3-(S-2-amino-2-cyclohexylmethyl)-acetamido-3-methyl-4-phenoxy-azetidine-2-one trifluoro acetic acid salt

A solution of (3S, 4R)-3-[2S-2-(tert-butoxycarbonyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one (0.51g, 1.15mmol) in dry methylene chloride (10ml) under nitrogen was cooled to 0 °C and treated with trifluoro acetic acid (4ml). The resulting solution was stirred between 15 to 20 0C for 1hr and evaporated in vacuo. The crude product obtained was further triturated with ether, then with hexanes, filtered and dried to give a white solid (0.464g).

Yield: 88.2%

Step-2: (3S, 4R)-3-[2S-2-(6-N, N-dibenzyloxycarbonylguanidino hexanoyl)- amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one

A mixture of 6-(N,N-dibenzyloxycarbonyl)-guanidino hexanoic acid (0.446g, 1.01mmol), DCC (0.208g, 1.01mmol) and 1-HBT (0.137g, 1.01mmol) in dry THF (35ml) was stirred under nitrogen, at room temperature for 1.5 hrs. The resulting suspension was cooled to 0 ^{0}C and filtered in to (3S, 4R)-3-(2S-2-amino-2-cyclohexylmethyl)-acetamido-3-methyl-4-phenoxy- azetidine-2-one trifluoro acetic acid salt (0.464g, 1.10mmol) in dry THF (15ml). The reaction mixture was treated with triethyl amine (0.112g, 1.11mmol), stirred for 2hrs., at room temperature and diluted with ethyl acetate (80ml). The EtOAc solution was washed with water, aq. sat. $NaHCO_3$ (2x80ml), brine solution, dried over magnesium sulfate and filtered. Evaporation of the solvent *in vacuo* gave the crude material which was purified by silica gel column using a mixture of hexane:ethyl acetate (3:7)to give the title compound (0.22g).

Yield: 28.3%; m.p.: 108-109 ^{0}C

^{1}H NMR (DMSO-d_6): ä 0.58-1.63(m, 22H), 2.00-2.20(m, 2H), 3.25-3.35(m, 2H), 4.33-4.42(m, 1H), 5.03(s, 2H), 5.21(s, 2H), 5.38(s, 1H), 6.76-7.41(m, 15H), 7.83(d, 1H, J=9.0 Hz), 8.00(s, 1H), 8.39(t, 1H, J=3.0 Hz), 8.96(s, 1H), 11.60(s, 1H).

Example-10

(3S, 4S)-3-[2S-2-(6-N, N-di-tert-butoxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-

one (0.714g, 2.188mmol) in dry THF (28ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.720) at 50psi over 2.5hrs. The resulting suspension was filtered through Celite in to a pre-filtered solution of benzotriazolyl-2-[6-(N, N-di-tert-butoxycarbonylguanidino hexanoyl)-amino-2-cyclohexyl methyl]-acetate, prepared by reacting a mixture of 2-[6-(N, N-di-tert-butoxycarbonyl guanidino hexanoyl)-amino-2-cyclohexyl methyl]-acetic acid (1.21g, 2.297mmol), DCC (0.474g, 2.297mmol) and 1-HBT (0.310g, 2.297mmol) in dry THF (30ml), at room temperature and stirring for 1.5hrs. The resulting reaction mixture was stirred at room temperature for 2hrs. and evaporated *in vacuo*. The crude product thus obtained was purified over silica gel column using a mixture of hexanes: ethyl acetate (3:7) to give the title compound (0.68g).

Yield: 44.4%; m.p.:119-121 °C

^{1}H NMR (DMSO-d_6): ä 0.80-1.75(m, 40H), 2.10-2.20(m, 2H), 3.20-3.30(m, 2H,), 4.40-4.50(m, 1H), 5.61(s, 1H), 6.85-7.35(m, 5H), 7.93(d, 1H, J= 5.0Hz), 8.25(t, 1H, J= 3.0Hz,), 8.27(s, 1H), 9.10(s, 1H), 11.51(s, 1H).

Example-11

(3S, 4R)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

A solution of (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.35g, 0.92mmol) in ethyl acetate (20ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.3g) at 50psi over 1.5hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-2-(N- benzyloxycarbonyl)-amino-3-phenylpropionate(CbzPhe) in dry THF, which is prepared by the reaction of N-(benzyloxycarbonyl)amino-phenylalanine (0.275g, 0.92mmol) in THF (6ml), with DCC (0.190g, 0.92mmol) and 1-HBT (0.124g, 0.92mmol) at 10 °C and stirring for 1.5hrs.,

followed by filtration. The reaction mixture was stirred at room temperature for 2 hrs., washed with aq. sat. sodium bicarbonate, followed by water, brine and dried over anhyd. sodium sulfate. Filtration followed by evaporation of the solvent in vacuo afforded the crude product, which was purified by silica gel column chromatography using a gradient mixture of ethyl acetate and hexanes (1:1 to 1:0) to give the title compound (0.160g).

Yield: 37%; m.p.: 103-105 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.55(s, 3H), 2.55-2.70(m, 2H), 4.23-4.34(m, 1H), 4.91(s, 2H), 5.46(s, 1H), 6.81-7.80(m, 15H), 7.55(d, 1H, J=1.5 Hz), 8.27(s, 1H), 9.05(s, 1H).

Example-12

(3S, 4S)-3-[2S-2-(N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.3g, 0.92mmol) in dry THF (30ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.3g) at 50 psi over 2 hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-2-(N- tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)-acetate in dry THF, which is prepared by the reaction of 2- (N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)-acetic acid (0.245g, 0.92mmol) in THF (20ml), with DCC (0.190g, 0.92mmol) and 1-HBT (0.124g, 0.92mmol) at 10 ^{0}C and stirring for 2hrs., followed by filtration. The reaction mixture was stirred at room temperature for 2hrs., and evaporated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using a gradient mixture of ethyl acetate and methanol (9.5: 0.5) to give the desired (3S, 4S)-3-[2S-2-(N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one (0.35g).

Yield: 86.4%; m.p.: 109-110 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.29(s, 9H), 1.33(s, 3H), 2.75-3.05(m, 2H), 4.26-4.40(m, 1H), 5.57(s, 1), 6.83-7.37(m, 7H), 7.68(d, 1H, J=7.9 Hz), 8.38(d, 1H, J=4.6 Hz), 8.48 and 8.52(2s, 2H), 9.17(s, 1H).

Example-13

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

Step 1 : (3S, 4S)-3-[2S-2-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one trifluoroacetate salt:

A solution of (3S, 4S)-3-[2S-2-(N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one (0.300g, 0.681mmol) in dry methylene chloride (8ml) under nitrogen was cooled to 0 ^{0}C. Then was added trifluoro acetic acid (6ml) and the reaction mixture was stirred at 0 ^{0}C for 2hrs and at room temperature for 1hr. The volatile solvents were evaporated in vacuo and the gum thus obtained was triturated with ether. The solid obtained was filtered and dried to give (3S, 4S)-3-[2S-2-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one trifluoroacetate salt (0.294g, 76%) as a solid.

^{1}H NMR (DMSO-d_6): ä 1.33(s, 3H), 3.12-3.25(m, 2H), 4.14(brs, 1H), 5.51(s, 1H), 6.82-7.46(m, 6H), 7.83(d, 1H, J=7.8Hz), 8.34(brs, 3H), 8.54-8.60(m, 3H), 9.05(s, 1H), 9.32(s, 1H).

Step2: (3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-

methyl-4-phenoxy azetidin-2-one

A solution of (3S, 4S)-3-[2S-2-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one trifluoroacetate salt (0.274g, 0.482mmol) in dry THF (30ml) under nitrogen was cooled to 0 ^{0}C, and was added triethyl amine (0.122g, 1.205mmol). With in 2min., N-(benzyloxycarbonyl)succinimide (0.132g, 0.5302mmol) was added to the reaction mixture and stirred at 0 ^{0}C for 1hr. The solvents were evaporated *in vacuo* and the crude product was dissolved in ethyl acetate (50ml). The ethyl acetate solution was washed with aq. sat. sodium bicarbonate, brine solution and dried over anhydr. sodium sulfate. Filtration followed by evaporation of the solvent *in vacuo* to give a gummy product, which was purified by silica gel chromatography using a mixture of EtOAc: MeOH (9:1) to give the title compound (0.16g).

Yield: 70% ; m.p.: 84-86^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.34(ms, 3H), 2.77-3.10(m, 2H), 4.33-4.50(m, 1H), 4.96(s, 2H), 5.57(s, 1H), 6.82-7.73(m, 13H), 8.40-8.50(m, 2H), 8.60(s, 1H), 9.18(s, 1H).

Example-14

(3S, 4R)-3-[2S-2-(N-tert-butoxycarbonylamino)-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

A solution of (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methy-4-phenoxy azetidin-2-one (0.176g, 0.54mmol) in dry THF (20ml) was hydrogenated in presence of 10%Pd-C (50% wet, 0.176g) at 50 psi over 2 hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-2-(N- tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)-

acetate in dry THF, which is prepared by the reaction of 2- (N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)-acetic acid (0.144g, 0.54mmol) in THF (20ml), with DCC (0.112g, 0.54 mmol) and 1-HBT (0.073 g, 0.54 mmol) at 10 ^{0}C and stirring for 2hrs., followed by filtration. The reaction mixture was stirred at room temperature for 2hrs. and evaporated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using a gradient mixture of ethyl acetate and methanol(9: 1) to give the desired (3S, 4R)-3-[2S-2-(N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one (0.069g).

Yield: 29%; m.p.: 94-96 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.29(s, 9H), 1.33(s, 3H), 2.75-3.05(m, 2H), 4.26-4.40(m, 1H), 5.57(s, 1), 6.83-7.37(m, 7H), 7.68(d, 1H, J=7.9 Hz), 8.38(d, 1H, J=4.6 Hz), 8.48 and 8.52(2s, 2H), 9.17(s, 1H).

Example-15

(3S,4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one.

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-acetoxy azetidine-2-one (1.302g, 4.4544mmol) in dry THF (35ml) was hydrogenated in presence of 10%Pd-C(50% wet, 1.30g) at 45 psi over 2 hrs. The resulting mixture was filtered through Celite in to a solution of benzotriazolyl-2-(N-benzyloxycarbonyl)-amino phenyl alanine in dry THF, which is prepared by the reaction of N(benzyloxycarbonyl)amido phenyl alanine (1.333g, 4.4544mmol) in (45ml), with DCC (0.919g, 4.4544mmol) and 1-HBT (0.602g, 4.4544mmol) at 10 ^{0}C and stirring for 1hr. The reaction mixture was stirred at room temperature for 1hr. and evaporated *in vacuo* to give the crude product. The above crude compound was purified over silica gel column, using a mixture of

hexane:ethyl acetate(2:3) to give (3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one.

Yield: 1.25g (63.8%) ; m.p.: 86-88 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.28(s, 3H), 2.10(s, 3H), 2.70-3.00(m, 2H), 4.30-4.40(m, 1H), 4.94(ABq, 2H, J=2.0Hz), 5.87(s, 1H), 7.22-7.34(m, 10H), 7.50(d, 1H), 8.45(s, 1H), 9.01(s, 1H).

Example-16

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-(benzothiazol-2-yl)-mercapto azetidine-2-one (16A) and (3S, 4R)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methy-4-(benzothiazol-2-yl)-mercapto azetidin-2-one (16B)

A solution of (3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one (0.286g, 0.651mmol) in a mixture of tetrahydrofuran(20ml) and water(5 ml) was cooled to 0 ^{0}C and treated with an aqueous NaOH(0.029g, 0.716mol in 15ml of water)solution of 2-mercaptobenzothiazole(0.131mg, 0.781mmol) drop wise over 10 min. The resulting solution after stirring at 0 ^{0}C for 1h. and at room temperature for 3 hr. was diluted with ethyl acetate(100ml) and brine solution(20ml). The aqueous layer was separated and the organic layer was washed with brine dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent in vacuo gave a gummy foam, which on purification over silica gel column (hexanes:ethyl acetate/ 2:3) resulted in the isolation of two diasteriomers.

a). (3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-

(benzothiazol-2-yl)-mercapto azetidine-2-one (0.028g).

Yield: 8%; m.p.: 83-85 °C

^{1}H NMR (DMSO-d6): ä 1.43(s, 3H), 2.75-3.10(m, 2H), 4.35-4.45(m, 1H), 4.96(ABq, 2H, J= 2.8Hz), 5.92(s, 1H), 7.15-7.50(m, 12H), 7.58(d, 1H, J= 8.7Hz), 7.87(d, 1H, J= 7.0Hz), 8.05(d, 1H, J= 7.0Hz), 8.61(s, 1H), 9.13(s, 1H).

b). (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methy-4–(benzothiazol-2-yl)-mercapto azetidin-2-one (0.03g).

Yield: 8.4%; m.p.: 108-110°C

^{1}H NMR (DMSO-d_6): ä 1.21(s, 3H), 2.71-3.24(m, 2H), 4.36-4.52(m, 1H), 4.95(ABq, 2H, J=8.9Hz), 5.77(s, 1H), 7.03-8.10(m, 15H), 8.70(s, 1H), 9.33(s, 1H).

Example-17

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-ones

Stem 1: (3S, 4S and 3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-(3–diphenylmethoxycarbonyl)-phenoxy azetidine-2-ones:

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-acetoxy azetidine-2-one (2.0g, 6.8mmol) in THF (15mml) was added drop wise to a stirred and cooled (0 °C) solution of 3-(diphenylmethoxycarbonyl)-phenol (3.1g, 10.2mmol) in a mixture of THF (30ml) and 1N. NaOH (8.7ml). The reaction mixture was stirred at 0 °C for 1hr., then at room temperature for 2hrs., and was diluted with ethyl acetate (250ml) and water (50ml). The organic layer was separated, washed with water followed by brine solution,

dried over anhydr. sodium sulfate, filtered and evaporated *in vacuo* to give the crude product as a gummy mass. Purification of the above gummy crude product over silica gel column chromatography using a gradient mixture of hexane: ethyl acetate (3:1 to 1:1) gave two diastereomers.

a): (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one:

^{1}H NMR (DMSO-d_6): ä 1.31(s, 3H), 5.06(s, 2H), 5.78(s, 1H), 7.05(s, 1H), 7.21-7.59(m, 18H), 7.82(1H, d, J=7.8Hz), 8.07(s, 1H), 9.22(s, 1H).

Yield: 0.9g (25%)

b): (3S, 4R)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-(3- diphenylmethoxycarbonyl)-phenoxyl azetidine-2-one:

^{1}H NMR (DMSO-d_6): ä 1.50(s, 3H), 4.98(ABq, 2H, J=21.6 and 12.0Hz), 5.61(s, 1H), 7.05-7.95 (m, 21H), 9.06(s, 1H).

Yield: 0.88g (24%)

Step 2: (3S, 4S)-3-amino-3-methyl-4-(3-carboxy)-phenoxy azetidine-2-one:

A solution of (3S, 4S)-3-(N-benzyloxycarbonyl)-amino-3-methyl-4-(3-diphenylmethanecarboxy)-phenoxy azetidine-2-one (0.9g, 1.68mmol) in ethyl acetate (20ml) was hydrogenated at 50psi, in presence of 10% Pd-C over 1.5hrs. The suspension was filtered through Celite and washed with ethyl acetate. The Celite bed was washed with a mixture of acetonitrile:water (1:1, 300ml), and the acetonitrile:water washings were concentrated to 60 ml, then lyophilized to give the amine as a white

solid (0.23g, 58%).

^{1}H NMR (DMSO-d_6): ä 1.17(s, 3H), 5.29(s, 1H), 7.21-7.63(m, 4H), 8.92(s, 1H).

Step 3: (3S, 4S)-3-amino-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one:

(3S, 4S)-3-amino-3-methyl-4-(3-carboxy)-phenoxy azetidine-2-one, obtained from step-2 was dissolved in acetone (30ml) and was added diphenyl diazomethane (0.19g, 0.97mmol) in acetone (10ml). After stirring over night, the volatiles were evaporated and the crude product obtained was purified by silica gel column chromatography using a gradient mixture of hexanes:ethyl acetate (2:1 to 0:1) to give the desired compound (0.22g).

Yield: 56%; m.p.: 142-144 ^{0}C

^{1}H NMR (DMSO-d_6): ä 1.16(s, 3H), 2.56(s, 2H), 5.31(s, 1H), 7.03(s, 1H), 7.35-7.59(m, 12H), 7.74(s, 1H), 8.93(s, 1H).

Step 3: (3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-diphenylmethoxycarbonyl)phenyl azetidine-2-ones

A solution of (3S, 4S)-3-amino-3-methyl-4-(3-diphenylmethanecarboxy)phenyl azetidine-2-one (0.060g, 0.15mol) in THF (3ml) was treated with N-(benzyloxycarbonyl)-phenyl alanine (0.045mg, 0.15mmol), DCC (0.031g, 0.15mmol) and 1-HBT (0.020g, 0.15mmol). The mixture was stirred at room temperature for 2 hrs. and was diluted with ethyl acetate. The ethyl acetate solution was washed with aq. sat. sodium bicarbonate solution followed by water and evaporated *in vacuo*. The crude product obtained was treated with ether and the solid obtained was filtered and dried give the title compound

(0.050g).

Yield: 49%; m.p.: 91-96 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 1.33(s, 3H), 2.75-3.12(m, 2H), 4.33-4.48(m, 1H), 4.95(ABq, 2H, J=3.0Hz), 5.64(s, 1H), 7.01(s, 1H), 7.13-7.60(m, 24H), 7.83(d, 1H, j+7.8Hz), 8.60s, 1H), 9.24(s, 1H).

Example-18

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one:

A solution of (3S, 4S)-3-amino-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one (0.060g, 0.15mmol) in dry THF (3ml) was treated with N-(3-phenylpropionyl)-amino phenyl alanine (0.44g, 0.15mmol), DCC (0.031g, 0.15mmol) and 1-HBT (0.020g, 0.15mmol). The reaction mixture was stirred at room temperature for 2hrs. and diluted with ethyl acetate (50ml). The ethyl acetate solution was washed with aq. sat. sodium bicarbonate solution followed by water and evaporated *in vacuo*. The crude product obtained was treated with ether and the solid obtained was filtered and dried to give the title compound (0.070g).

Yield: 69%; m.p.: 91-95 ^{0}C

^{1}H NMR (DMSO-d_6): ä 1.20(s, 3H), 2.32-2.40(m, 2H), 2.68-3.05(m, 4H), 4.65-4.75(m, 1H), 5.60(s, 1H), 7.05-7.53(m, 24H), 7.86(d, 1H, J=7.8Hz), 8.18(d, 1H, J=8.7Hz), 8.60(s, 1H), 9.26(s, 1H).

Example-19

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-carboxy)-phenoxy azetidine-2-one:

To a cooled (0 °C) and stirred solution of (3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one (0.060g, 0.038mmol) in dry methylene chloride (2ml) was added with trifluoro acetic acid (1ml) and anisole (2 drops). The reaction mixture was stirred at 0 °C for 0.5hr., and evaporated *in vacuo*. The crude product obtained was treated with a mixture of ether:hexanes (1:1) to give a solid, which was filtered and dried (?) to give the title compound (0.025g).

Yield: 55%; m.p.: 120-122 °C.

^{1}H NMR (DMSO-d_6): ä 1.32(s, 3H), 2.35-2.39(m, 2H), 2.65-3.14(m, 4H), 4.67-4.78(m, 1H), 5.62(s, 1H), 7.14-7.65(m, 14H), 8.13(d, 1H, J=8.8Hz), 8.61(s, 1H), 9.20(s, 1H).

Example-20

(3S, 4S)-3-{2S-2-[5-[-1-piperazine-4-(pyrimidin-2-yl)-5-oxo-pentanoyl)-amino-2-isopropyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one:

A solution of (3S, 4S)-3-[2S-2-(benzyloxycarbonyl)-amino-2-isopropyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one (0.100g, 0.227mmol) in a 1:1 mixture of ethyl acetate and THF (15ml) was hydrogenated at 50psi, over 1.5hrs., in presence of 10% Pd-C (50% wet). The resulting suspension was filtered through Celite and the filtrate was evaporated *in vacuo* to give the amine, which was dissolved in DMF (5ml) and stirred

under nitrogen. Glutaric anhydride (0.026g, 0.227mmol) was added to the above reaction mixture in one portion and after stirring at room temperature for 1hr., was added HOBT (0.030g, 0.227mmol) followed by DCC (0.047g, 0.227mmol). After stirring for 0.5hrs., the reaction mixture was treated with 4-(pyrimidin-2-yl)piperazine dihydrochloride (0.054g, 0.227mmol) followed by triethyl amine ( ). The reaction mixture was stirred at room temperature for 2hrs., then diluted with ethyl acetate (50ml) and water (50ml). The organic layer was separated, washed with water, aq. sat. sodium bicarbonate, brine solution, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The crude product obtained was treated with ether and the solid obtained was, filtered and dried to give the title compound (0.01g).

Yield: 8%; m.p.: 115-120 °C.

^{1}H NMR (DMSO-d_6): ä 0.87(d, 3H, J=6.1Hz), 0.92(d, 3H, J=6.3Hz), 1.32(s, 3H), 1.20-2.39(m, 12H), 3.52(brs, 2H), 3.72(brs, 3H), 4.40-4.52(m, 1H), 5.62(s, 1H), 6.64(t, 1H, H=4.7Hz), 6.85-7.37(m, 5H), 8.00(d, 1H, J=8.0Hz), 8.37 and 8.39(2s, 2H), 8.46(s, 1H), 9.09(s, 1H).

Example-21

(3S, 4S)-3-[2S-2-(2R-benzyloxycarbonyl)-amino2-phenyl)-acetamido-2-isopropyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one

A solution of (3S, 4S)-3-[2S-2-(benzyloxycarbonyl)-amino-2-isopropyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one (0.24g, 0.54mmol) in THF (15ml) was hydrogenated at 50psi, over 1.5hrs. in presence of 10% Pd-C (50% wet). The resulting suspension was filtered through Celite in to a solution of benzotriazolyl-N-(benzyloxycarbonyl)-D-phenyl glycine in THF (5ml), prepared by reacting N-benzyloxy carbonyl-D-phenyl glycine (0.155g, 0.54mol), DCC (0.112g, 0.54mmol) and 1-HBT (0.73g, 0.54mmol) in dry THF for 1.5hr., followed by filtration. The reaction mixture was stirred at room temperature for 2hrs, diluted with ethyl acetate (80ml) and the organic layer was

separated. The ethyl acetate solution was washed with aq. sat. sodium bicarbonate, brine solution, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The solid obtained was treated with ether filtered and dried to give the desired compound (0.200g).

Yield: 64%; m.p.: 117-120 ^{0}C.

^{1}H NMR (DMSO-d_6): ä 0.63(d, 3H, J=6.0Hz), 0.77(d, 3H, J=6.0Hz), 0.78-0.95(m, 1H), 1.36(s, 3H), 1.26-1.50(m, 2H), 4.25-4.40(m, 1H), 4.90(ABq, 2H, J=12.5 and 17.2Hz), 5.33(d, 1H, J=7.6Hz), 5.63(s, 1H), 6.85-7.50(m, 15H), 8.01(d, 1H, J=7.5Hz), 8.29(s, 1H), 8.56(d, 1H, J=9.0Hz), 9.12(s, 1H).

Biological Example

Compounds of the invention were shown to be inhibitors of cathepsins B and/or L and/or K and/or S by testing according to the following assays.

Assay procedure for Cathepsin K

To 170µl of enzyme-buffer mixture (r Cathepsin K diluted to give approx. 30 F units/min. Buffer: 100mM sodium acetate, 5 mM EDTA, 20 mM L-Cysteine, 0.01% Brij , pH 5.5), 10µl of inhibitor (dissolved in 100 % DMSO) was added.

After 10 min of incubation at room temperature 20µl of 2.7 mM substrate (N-CBZ-Phe-Arg-AMC, dissolved in DMSO) was added to initiate reaction. Reading is followed for 10min at the Fluoroscan II plate reader (excitation at 380nm, emission at 460nm).

A plot of percentage of inhibition vs inhibitor concentration is obtained, and the IC50 is determined using a linear regression calculation (concentration of inhibitor which

will give 50% inhibition).

Assay procedure for Cathepsin S

To 170µl of enzyme-buffer mixture (r Cathepsin S diluted to give approx. 30 F units/min, buffer: 100mM sodium phosphate, 1 mM EDTA, 5 mM DTT ,0.01% Brij, pH 6.5.), 10µl of inhibitor (dissolved in 100 % DMSO) was added.

After 10 min of incubation at room temperature 20µl of 1.2 mM substrate (CBZ-Val-Val-Arg- AMC, dissolved in DMSO) was added to initiate reaction. Reading is followed for 10min at the Fluoroscan II plate reader (excitation at 380nm, emission at 460nm).

A plot of percentage of inhibition vs inhibitor concentration is obtained, and the IC50 is determined using a linear regression calculation (concentration of inhibitor which will give 50% inhibition).

Assay procedure for Cathepsin B

To 170µl of enzyme-buffer mixture (r Cathepsin B diluted to give approx. 30 F units/min, buffer: 56mM Na acetate, 1.124 mM EDTA, 10 mM DTT, pH 5.1), 10µl of inhibitor (dissolved in 100% DMSO) was added.

After 10 min of incubation at room temperature 20µl of 5mM substrate (N-CBZ-Phe-Arg-AMC, dissolved in DMSO) was added to initiate reaction. Reading is followed for 10 min at the Fluoroscan reader (excitation at 380nm, emission at 460nm).

A plot of percentage of inhibition vs inhibitor concentration is obtained, and the IC50 is determined using a linear regression calculation (concentration of inhibitor which will give 50% inhibition).

Assay procedure for Cathepsin L

To 170µl of an enzyme-buffer mixture (enzyme: r Cathepsin L , diluted to give approx. 25 F units/min, buffer: 58.8 mM Na citrate, 1.18 mM EDTA, 235 mM sodium chloride, 10 mM DTT, pH 5.0), 10µl of an inhibitor (dissolved in 100% DMSO) was added.

After 10 min of incubation at room temperature 20µl of 1 mM substrate (N-CBZ-Phe-Arg-AMC) dissolved in DMSO was added to initiate the reaction. Reading was followed for 10 min at the Fluoroscan reader (excitation at 380 nm, emission at 460 nm).

A plot of percentage of inhibition vs inhibitor concentration is obtained, and the IC50 is determined using a linear regression calculation (concentration of inhibitor which will give 50% inhibition).

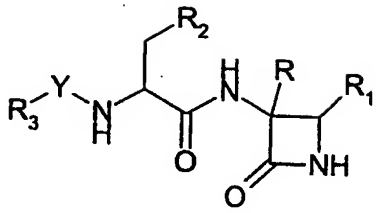
Results: The IC_{50}'s for the compounds of Examples 4, 7, 12, 14 and 18 are shown in Table 1. The IC_{50}'s of the other compounds of the examples were generally <50µM in the case of cathepsin B; <40µM in the case of cathepsin L; <40µM in the case of cathepsin K; and <10µM in the case of cathepsin S.

Table-1. In vitro inhibitory activity of test compounds (IC50's - µM)

Example	CatB IC50	CatL IC50	CatK IC50	CatS IC50
4	10.04	1.91	1.14	0.098
7	26.24	32.51	32.51	0.02
12	11.35	2.27	7.74	1.8
14	0.36	0.45	1.34	0.05
18	>36.6	7.33	7.3	0.69

Claims:

1. A compound of formula (I)



(I)

Y represents -C(O)- or -S(O_2)-;

R represents an allyl (ie CH_2=$CHCH_2$-) group or a radical of formula R_4-$(ALK)_p$-$(Z)_n$-$(ALK)_q$- wherein Z represents -O- or -S-, ALK represents a divalent C_1-C_3alkyl or halogen-substituted C_1-C_3alkyl radical, R_4 represents hydrogen or halogen, or an optionally substituted phenyl group, and n, p and q are independently 0 or 1, PROVIDED THAT (i) when R_4 is hydrogen and both p and n are 0 then q is 1; and (ii) when R_4 is halogen and n is 1 then p is 1; and (iii) when R_4 is halogen then p, n and q are not all 0;

R_1 represents -$OCOR_5$, -OR_5, -SR_5, -S(O)R_5, or -$S(O)_2R_5$;

R_2 represents a radical of formula R_6-$(ALK)_p$-$(Z)_n$-$(ALK)_q$- wherein p, Z and ALK are as defined in relation to R, q is 0 or 1, n is 0 or 1 when q is 1 and n is 0 when q is 0, and R_6 is hydrogen or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclic group; or R_2 together with the carbon atom to which it is attached forms a cycloalkyl ring;

R_3 represents -OR_5 or -R_5;

R_5 represents a radical of formula R_7-$(A)_t$- wherein t is 0 or 1; A represents (i) an

optionally substituted divalent C_1-C_6alkyl, radical which may be interrupted by one or more non-adjacent -O-, -S- or -NH- linkages, or (ii) a divalent C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclic radical, or (iii) a -NH- link; and R_7 represents hydrogen or an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclic group;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A compound as claimed in claim 1 wherein Y is -C(O)-.

3. A compound as claimed in claim 1 or claim 2 wherein R is allyl, methyl, ethyl, n-propyl, n-or iso-butyl, methyoxymethyl, ethoxymethyl, benzyl, or phenoxymethyl.

4. A compound as claimed in any of the preceding claims wherein R_1 is acetoxy; butyloxy; 2-carboxyethyloxy; 2-aminoethyloxy; 2-fluoroethoxy; cyclopentyloxy; cyclohexyloxy; cyclohexylthio; phenoxy, phenoxy substituted by methyl, tert-butyl, trifluoromethyl, amino, hydroxy, acetamido, cyano, carboxy or fluoro; naphthyloxy; morpholino-phenyloxy; 2-hydroxyethylthio; phenylthio; phenylsulphonyl; 4-(2-carboxy-2-amino ethyl)-phenoxy; 2-pyridylthio; 4-pyridylthio; benzyloxy; 3-pyridyl-phenoxy; 3-tetrazolyl-phenoxy; 3,4-methylenedioxy-phenoxy; 3,4-ethylenedioxy-phenoxy; tetrahydroquinolinoxy; quinolinoxy; or quinolinthio.

5. A compound as claimed in any of the preceding claims wherein R_2 is a phenyl group which may be substituted by one or more of hydroxy, halogen, methoxy, methyl, isopropyl, tert-butyl and trifluoromethyl; isopropyl, cyclohexyl; 3-pyridinyl; naphthyl; biphenyl; 2-thienyl; 3,4-methylenedioxyphenyl; 3,4-ethylenedioxy -phenyl; benzothienyl; thiazolyl; quinolinyl; isoquinolinyl; tetrahydroquinolinyl; tetrahydronaphthyl; aminonaphthyl; or acetamidonaphthyl.

6. A compound as claimed in any of the preceding claims wherein R_3 is

benzyloxy, 3-phenylpropyloxy, 3-phenylpropyl, 3-phenylprop-1-enyl, 6-N,N-dibenzyloxycarbonylguanidino-hexyl, 6-guanidino-hexyl, methoxy-methyleneoxy-methyl, 2-amino-ethoxy-methyl, 3-(pyridin-3- or 4-yl)-propyl, or 3-(pyridin-3- or 4-yl)-prop-1-enyl.

7. A compound as claimed in any of the preceding claims wherein the R and R_1 groups are cis to each other.

8. A compound as claimed in claim 1, selected from the group consisting of:

(3S, 4S)- 3-[2S-2-(benzyloxycarbonylamino)-2-benzyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one

(3S, 4S)-3-[2S-2-(benzyloxycarbonylamino)-2-isopropyl]-acetamido-3-methyl -4-phenoxy azetidin-2-one

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-isopropyl]-acetamido-3-benzyl -4-phenoxy azetidin-2-one

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one.

(3S, 4R)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one

(3S, 4S)-3-[2S-2-(6-N, N-dibenzyloxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one

(3S, 4R)-3-[2S-2-(tert-butoxycarbonyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one.

(3S, 4R)-3-[2S-2-(6-N, N-dibenzyloxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one

(3S, 4S)-3-[2S-2-(6-N, N-di-tert-butoxycarbonylguanidino hexanoyl)-amino-2-cyclohexylmethyl]-acetamido-3-methyl-4-phenoxy- azetidine-2-one

(3S, 4R)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

(3S, 4S)-3-[2S-2-(N-tert-butoxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

(3S, 4R)-3-[2S-2-(N-tert-butoxycarbonylamino)-2-(pyridin-3-yl)]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-acetoxy azetidine-2-one.

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-(benzothiazol-2-yl)-mercapto azetidine-2-one

(3S, 4R)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methy-4-(benzothiazol-2-yl)-mercapto azetidin-2-one

(3S, 4S)-3-[2S-2-(N-benzyloxycarbonyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-diphenylmethoxycarbonyl)-phenoxy azetidine-2-one:

(3S, 4S)-3-[2S-2-(3-phenylpropionyl)-amino-2-benzyl]-acetamido-3-methyl-4-(3-carboxy)-phenoxy azetidine-2-one:

(3S, 4S)-3-{2S-2-[5-[-1-piperazine-4-(pyrimidin-2-yl)-5-oxo-pentanoyl)-amino-2-isopropyl]-acetamido-3-methyl-4-phenoxy azetidine-2-one:

(3S, 4S)-3-[2S-2-(2R-benzyloxycarbonyl)-aminoB2-phenyl)-acetamido-2-isopropyl]-acetamido-3-methyl-4-phenoxy azetidin-2-one.

and pharmaceutically acceptable salts, hydrates and solvates thereof.

9. A pharmaceutical composition comprising of compound as claimed in any of the preceding claims together with a pharmaceutically acceptable carrier.

10. A method of treatment of diseases susceptible to amelioration by inhibition of cysteine protease activity, comprising administration to the patient of an amount of a compound as claimed in any of claims 1 to 8 effective to inhibit such activity.

11. A method as claimed in claim 10 wherein the disease is muscular dystrophy, osteoporosis, tumour metastasis, rheumatoid arthritis, neuronal or cardiac ischaemia, allergic immune response, or protozoal or bacterial disease.

INTERNATIONAL SEARCH REPORT

Int. donal Application No
PCT/GB 00/01261

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D205/085 A61K31/395 C07D401/12 A61K31/44 C07D417/12
C07D403/12 A61K31/505 A61P21/00 A61P19/00 A61P35/00
A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 48911 A (REDDY ANDHE VENKAT NARENDER ;ZHOU NIAN (CA); SINGH RAJESHWAR (CA);) 30 September 1999 (1999-09-30) claim 1 ---	1-11
X	WO 98 12176 A (SYNPHAR LAB INC) 26 March 1998 (1998-03-26) cited in the application claim 1 ---	1-11
X	WO 98 12210 A (SYNPHAR LAB INC ;CANADA NAT RES COUNCIL (CA)) 26 March 1998 (1998-03-26) cited in the application claim 1 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2000	28 June 2000 (28.06.00)

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gettins, M

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INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/GB 00/01261

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 32408 A (SYNPHAR LAB INC) 17 October 1996 (1996-10-17) cited in the application claim 1	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/GB 00/01261

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10 and 11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/01261

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